TAB C

FDA BIOEQUIVALENCE HEARING

Session III
Presenter: Leslie Z. Benet, Ph.D.
President, American Association of Pharmaceutical Scientists
"Criteria for Bioequivalence"

DR. LESLIE Z. BENET: Thank you, Mr. Commissioner. I'm the President of the American Association of Pharmaceutical Scientists, representing 2,468 members!! I want to thank the 41 members who joined yesterday!

As I did in the last two sessions, I'll speak on each of the topics listed in the document in the Federal Register. Reading from the task force comment on the +/-20% rule: The percent difference allowed should depend upon the drug and/or assay variability and types of statistics used. Twenty percent is an acceptable starting point. Minority task force opinion was for 10%. In the absence of information on drug variability, 20% will be acceptable if reviewed and recommended by the outside advisory panel for bioavailability/bioequivalence. The percent difference should not be an arbitrary decision of the medical officer only.

Now, in the text of our report which will be available tomorrow, it will also state under this section: President Benet to comment on poor scientific basis of those who attack the regulations by stating that FDA allows drug products to enter the market as generic equivalents with 80% and 120% of innovator's products, thus allowing a two-fold change from product to product. Such statements always ignore the fact that such theoretical product must not be statistically different from the innovator's product.

Those who state that there is a potential for a two-fold difference in bioavailability, switching from one generic product to another, are fooling themselves and, more importantly, fooling the public. That is a fallacious statement that does not go along with what the Regulations state. The Regulations state that they should not be statistically different, and if they are not statistically different, you are allowed to have a range that goes from 80% to 120%. To assume that a product would be approved by the FDA that could be 80% different and 120% different is nonsense. That is not feasible. Dr. Dighe has stated even when they are not statistically different and they are at 80% and 120%, he goes to the medical officer. But the rules state that they must show with appropriate power that these products are not different. Under those conditions, the variation can go from 80% to 120%.

If a product falls in that range, what it means is that the variability of one or both of the products -- and most likely it

is the drug itself as opposed to the drug product, as with the example of furosemide -- what it means is that the variability is so great from that particular drug in the population that is tested that you cannot see the difference, even though on the means there is the possibility of having a large difference.

Now, we're fooling the public and indicating to them that we do not have adequate controls and supervision by the FDA when we make those kinds of statements, and they're not true. That is not the basis of what the regulations state, and I'm really surprised that in today's situation in terms of scientific investigation and how we look at data, that those kinds of statements are being made freely and indicating that such a possibility does exist. I don't believe it exists.

Next is intra- and inter-subject variability: The task force comment is: normal crossover designs are generally recommended. However, existing crossover designs do not directly address intra-subject variability. Additional work is needed to define the database on variability. If a drug has high variability, or if a known intra-subject variability exists, then a more elaborate study design is desirable. For example, repeated subjects design or the use of stable isotopes.

Point No. 3 in the Federal Register: clinical significance of bioequivalence criteria, and No. 4: how closely should bioequivalence limits be set to clinical significant limits? Task force comment:

Both Nos. 3 and 4 are combined. Drugs with narrow therapeutic windows or with toxicity problems should possibly have more narrow bioequivalence limits. The task force suggested that the limits be recommended by the outside advisory panel for bioavailability/bioequivalence as described in Topic No. 5.

Justification for repeating clinical efficacy and safety studies: The task force comment -- If no bioavailability-bioequivalence studies are available or not feasible, or if the differences in bioequivalence are beyond the percentage allowed as recommended by the outside advisory panel for bioavailability-bioequivalence, then safety and efficacy must be assessed. In vitro dissolution is not an adequate substitute for in vivo bioequivalence.

The last area under this topic: reformulations. Types of changes that would trigger an in vivo bioequivalence study. Task force comment: For major changes, for example, changing an excipient in the formulation, bioequivalence is required. For minor changes, changing the amount of excipient as allowed within NDA specification, dissolution testing will be sufficient if correlation of the dissolution rate with bioavailability is available, or if the dissolution limits were set on the basis of bioavailability studies. It is also recommended that generic formulations be allowed to have ranges such as those in NDA